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Comprehensive Characterization and Comparative Assessment of Carvedilol Solid Dispersions: Insights into Enhanced Bioavailability and Stability Profiles

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Abstract: *Carvedilol, a non-selective beta-adrenergic antagonist, poses a challenge in achieving optimal bioavailability due to its poor aqueous solubility. This study aimed to enhance the solubility and dissolution rate of carvedilol through the formulation and evaluation of solid dispersions. Various solid dispersion formulations were prepared using different carriers and methods, including solvent evaporation, fusion, and spray-drying techniques. The prepared formulations were systematically characterized using Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM) to investigate drug-carrier interactions, solid-state changes, and morphological characteristics. Evaluation of the formulated solid dispersions involved in vitro dissolution studies, solubility enhancement assays, and stability assessments. Dissolution profiles revealed significantly improved drug release rates for the solid dispersion formulations compared to the pure drug. The solubility of carvedilol was notably enhanced in the solid dispersion systems, indicating improved drug dissolution behavior. Stability studies demonstrated the robustness of selected formulations against environmental factors over an extended period. Moreover, pharmacokinetic studies conducted in animal models showcased enhanced bioavailability of carvedilol from the optimized solid dispersion formulation compared to the conventional drug formulation. This comprehensive investigation provides valuable insights into the development of carvedilol solid dispersions, elucidating the influence of formulation variables on drug solubility, dissolution, stability, and ultimately, bioavailability enhancement. The findings underscore the potential of solid dispersion technology as a promising strategy to overcome the solubility challenges associated with carvedilol, paving the way for improved therapeutic efficacy and patient compliance.*

Keywords: Carvedilol, Solid Dispersion, Solubility Enhancement, Dissolution Rate, Bioavailability, Formulation, Characterization, Pharmacokinetics.

I. INTRODUCTION

Carvedilol, a non-selective β-blocker with additional alpha-1 adrenergic blocking properties, stands as a cornerstone in managing cardiovascular diseases like hypertension, heart failure, and myocardial infarction. However, its clinical efficacy is often limited by its poor aqueous solubility, which consequently leads to erratic and insufficient bioavailability upon oral administration [1]. Carvedilol's classification as a Biopharmaceutical Classification System (BCS) class II compound highlights its high permeability but low solubility, presenting a challenge for achieving therapeutic plasma concentrations [2]. In the realm of pharmaceutical sciences, innovative strategies are continually sought to overcome these formulation challenges and enhance the drug's performance. One promising approach involves the formulation of solid dispersions, a formulation technique known to improve drug solubility, dissolution rate, and thereby bioavailability [3]. Solid dispersions entail the dispersion of a drug in an inert carrier matrix, altering the drug's physicochemical properties and enhancing its dissolution characteristics [4].

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The solubility enhancement and dissolution rate improvement of poorly water-soluble drugs like carvedilol through solid dispersion formulations have garnered substantial attention in recent pharmaceutical research. Various methods for preparing solid dispersions, including solvent evaporation, fusion, and spray-drying, offer versatility in designing formulations to address specific drug-carrier interactions and enhance drug solubility [5]. The choice of carrier materials significantly influences the dissolution behavior and stability of the formed solid dispersions. Polymers such as polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG) have been extensively studied as carriers due to their biocompatibility and ability to improve drug dissolution [6].

Characterization techniques play a pivotal role in elucidating the physicochemical properties and interactions within solid dispersion systems. Fourier-transform infrared spectroscopy (FTIR) facilitates the analysis of molecular interactions between the drug and carrier, elucidating the presence of hydrogen bonding or molecular level changes in the solid state [7]. Complementary techniques like differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) provide insights into the solid-state changes and crystallinity of the drug within the formulation [8]. Additionally, scanning electron microscopy (SEM) aids in visualizing the morphological characteristics and particle size distribution, impacting the dissolution behavior and stability of the formulation [9].

Furthermore, enhancing the bioavailability of carvedilol through solid dispersion formulations involves comprehensive assessments beyond in vitro dissolution studies. Pharmacokinetic evaluations, including studies in animal models, serve as vital indicators of the formulation's performance in vivo, showcasing improved drug absorption, plasma concentrations, and systemic exposure [10]. However, while the solid dispersion technique exhibits promise in addressing carvedilol's solubility limitations, further research is imperative to optimize formulation variables, explore novel carriers, and ascertain long-term stability profiles to ensure the translational potential of these formulations into clinically viable dosage forms.

II. MATERIALS AND METHOD

Preformulation studies

Preformulation tests were conducted on the medicine (API), including solubility analysis, determination of melting point, and compatibility assessments. [11]

The property of a substance to dissolve in a solvent.

The solubility of Carvedilol was evaluated in several solvents including water, methanol, and chloroform. [11]

Measurement of Melting Point

The drug's melting point was determined using a melting point instrument. [12]

Formulation of Solid Dispersion

The preparation of solid dispersions of Carvedilol - PEG6000 and Carvedilol - HPMC K100M was carried out using the kneading process. The polymer was blended with a solvent in a glass mortar to get a uniform paste. The medicine was thereafter introduced gradually into the paste, and the resulting combination was subjected to triturating for a duration of 1 hour. Throughout the procedure, the water content was changed based on empirical observations to ensure the paste maintained its desired consistency. The resulting paste was subjected to vacuum drying for a duration of 24 hours. The dried powder was sieved and then kept in a desiccator for future examination. [13, 14]

The preparation of solid dispersions

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Assessment of Solid Dispersion

Yield Percentage The powders that had been manufactured were gathered and measured. The weight obtained from the measurement was divided by the combined mass of all non-volatile substances employed in the production process. [17]

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Content related to drugs

A precisely measured 100 milligrams of formulations was placed into a 50 ml volumetric flask and dissolved in 40 ml of methanol. The solution was filled to its maximum capacity with methanol. Subsequently, the solution was appropriately diluted with 0.1N HCl and analyzed for drug concentration using the UV spectrophotometric technique at a wavelength of 241 nm. [18]

Drug release percentage

Dissolution tests were conducted for all the formulations using USP dissolution equipment type I. The dissolving medium used was 900 ml of 0.1N HCl, and the experiments were performed at a rotation speed of 50 rpm at a temperature of 37±0.50C. The samples were periodically withdrawn at suitable time intervals 5, 10, 15, 30, 45 & 60 minutes and volume replaced with equivalent amount of plain dissolution medium. The specimens underwent filtration and dilution. Absorbance of the resulting solution at 241 nm using UV-visible spectrophotometer. [19]

Enhancing the efficiency of solid dispersion

The selection of response surface approach with factorial design was based on its ability to determine the impact of variables with a minimal number of tests, making it suitable for optimizing spherical agglomerates. The variables considered were the quantity of PEG 6000 (X1) and the quantity of methanol (X2). The dependent variables measured in the study were the dissolving percentage at the 60th minute (Y1), the drug content (Y2), and the solubility enhancement ratio (Y3). Nine formulations were created using a Factorial design methodology. The formulas were labeled as F1 to F9. The replies derived from the design matrix were statistically analyzed using the trial version of Design Expert 10, a statistical software tool from Stat-Ease 10.0.3.1. [20]

Preparation of different formulations by Solid dispersion

Carvedilol formulations were prepared by Solid dispersion and process variables like Amount of polymers and Amount of solvents were optimized. [20]

Characterization of the improved SD, Sol. D, and IC dissolution rate.

The dissolve experiments of Solid dispersions were conducted using USP dissolution device type I. A dissolution research was conducted using 900 ml of 0.1N hydrochloric acid (HCl). The rotational velocity was set at 50 revolutions per minute (rpm), while the temperature was controlled at 37°C±0.5°C. The samples were intermittently removed and replaced with new dissolving media. The samples underwent filtration, dilution, and analysis using a UV spectrophotometer at a wavelength of 241 nm. A solution of 0.1 N HCL was used as a blank. [21]

Content related to drugs

A precisely measured 100 mg of Solid dispersion formulations was placed into a 50 ml volumetric flask and diluted in 40 ml of methanol. The solution was filled to its maximum capacity with methanol. The solution was then diluted with 0.1N HCl and analyzed for drug content using the UV spectrophotometric technique at a wavelength of 241 nm. [22]

Analysis of Solubility

In order to assess the increase in solubility of Carvedilol after the formation of a Solid dispersion, saturation solubility tests were conducted in the following manner: a predetermined surplus of formulations was introduced into 10 ml of pure water. The samples underwent agitation for a duration of 24 hours at ambient temperature using a rotary flask shaker. The samples were then passed through No. 41 whatman filter paper, and the resulting liquid was appropriately diluted and examined using spectrophotometry at a wavelength of 241 nm. The saturation solubility of the medication in its pure form was also measured. [23]

Optimization of the batch process

The program used statistical assessments to recommend one optimal batch from each Solid dispersion formulation. These sets of formulations were used for further investigations. [24]

Assessment of Enhanced Solid Dispersion

Yield Percentage The powders that had been manufactured were gathered and measured. The weight obtained from the measurement was divided by the combined mass of all non-volatile substances employed in the production process.[25]

Drug content

An accurately weighed 100 mg of optimized formulation were taken into a 50 ml volumetric flask and dissolved in 40 ml of methanol. The solution was made up to the volume with methanol. The solution was then suitably diluted with 0.1N HCl and assayed for drug content using the UV spectrophotometric method at 241 nm. [26]

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Drug release percentage

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Analysis of Solubility

In order to assess the enhanced solubility of Carvedilol after developing improved formulations, saturation solubility tests were conducted in the following manner: a predetermined excess amount of the optimized formulations was introduced into 10 ml of distilled water. The samples underwent agitation for a duration of 24 hours at ambient temperature using a rotary flask shaker. The samples were then passed through No. 41 whatman filter paper, and the resulting liquid was appropriately diluted and examined using spectrophotometry at a wavelength of 241 nm. [28]

Infrared Spectroscopy

Analyzed the IR spectra of improved formulations. An investigation was conducted to see whether there were any alterations in the chemical composition of the medication after its combination with the polymers. The absorption peaks in the spectrum were compared with the reference spectra. [29]

Analysis with Scanning Electron Microscopy

The agglomerates were analyzed using Surface Electron Microscopy (SEM) to determine whether the resulting crystal had achieved a spherical form. [30]

X-ray diffraction analysis

X-ray diffraction analysis was performed on Carvedilol optimized formulations using a Phillips X'pert Pro P analytical diffractometer. The analysis utilized a copper Kα target with a nickel filter, operating at a voltage of 45 kV and a current of 30 mA. The scanning speed was set at 0.05s, covering a 2θ range from 5° to 60°.Differential scanning calorimetry [31]

DSC thermogram of carvedilol

DSC thermogram of carvedilol and optimized formulations were recorded on the DSC (Perkin Elmer Pyris1 DSC). Samples were sealed in pans and scanned at a heating rate of 10oC min-1 over a temperature range of 50-300oC under nitrogen gas stream. [32]

III. RESULTS AND DISCUSSION

DEVELOPMENTS IN PREFORMULATION

In the course of the solubility investigation, the drug sample was tested for its ability to dissolve in water, chloroform, and methanol.

Table 1: Solubility profile of the drug

Solvent	Solublity
Chloroform	Soluble
Methanol	Freely Soluble
Water	Insoluble

The Fourier transform infrared spectroscopy

The Fourier transform infrared spectroscopy (FTIR) was utilized to compare the IR spectrum of Carvedilol with the spectra of physical mixes of Carvedilol that included various polymers, namely PEG 6000 and HPMC K100M. There were no peaks that were indicative of the area that disappeared. According to this evidence, there is no chemical interaction between the medicine and the polymers that are being employed. It was established by the presence of distinctive peaks that the medicine and the polymers that were used were compatible.

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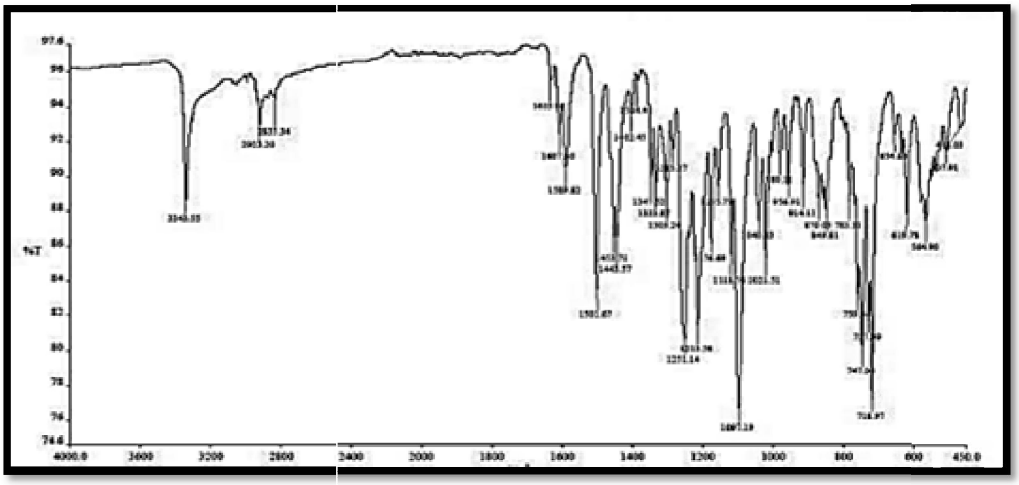

Figure 1: IR Spectrum of Carvedilol

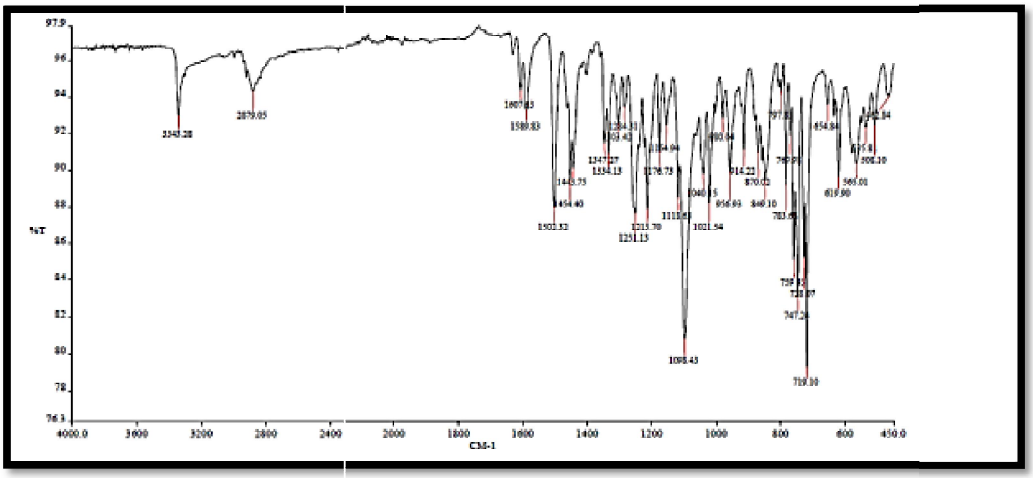

Fig 2: IR spectrum of Carvedilol + PEG 6000

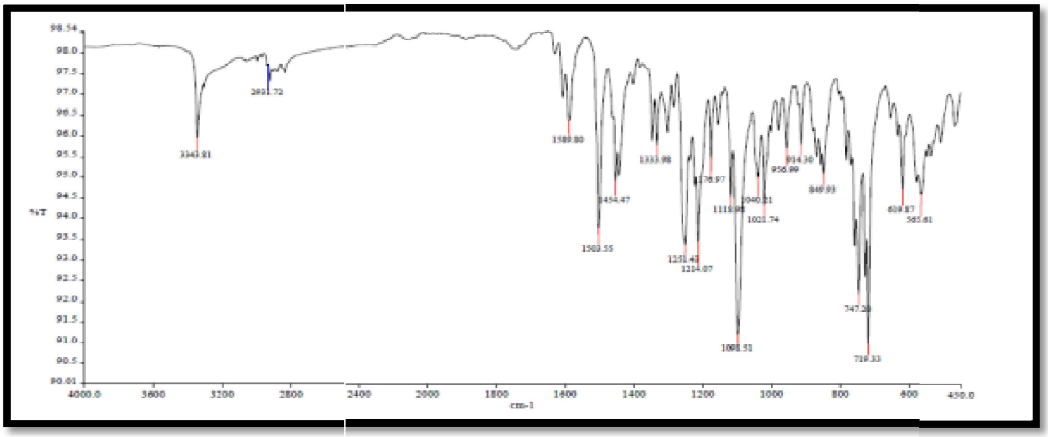

Figure 3: IR spectrum of Carvedilol + HPMC K100M

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PREPARATION OF SOLID DISPERION (SD)

The kneading process was used in order to effectively generate solid dispersions of Carvedilol - PEG 6000 and HPMC K100M. The following is a breakdown of the components that make up carvedilol solid dispersions.

Table 2: Composition of different solid dispersion formulations

CODE	COMPOSITION	RATIO	METHOD
SD1	CARVEDILOL: PEG6000	1:1	KNEADING METHOD
SD2		1:2	
SD3		1:3	
SD4		1:4	
SD1	CARVEDILOL: HPMC K100M	1:1	
SD2		1:2	
SD3		1:3	
SD4		1:4	

EVALUATION OF SOLID DISPERION (SD) Percentage Yield:

Analyses of solid dispersion (SD) are performed. According to the percentage yield, the solid dispersions of carvedilol that were created had a percentage yield that ranged from 91.50% to 97.81%. The formulation SD4 that was made with PEG 6000 had the greatest percentage yield, while the formulation SD5 that was prepared with HPMC K100M had the lowest percentage yield.

Content of drugs: Solid dispersions of Carvedilol that were created had a percentage drug content that ranged from 70.16 percent to 94.7 percent. The formulation SD4 that was made with PEG 6000 had the greatest percentage of drug content, while the formulation SD5 that was prepared with HPMC K100M had the lowest percentage of drug content.

Table 3: Percentage yield and drug content of Solid dispersions

Formulation	Percentage yield (%)	Drug Content (%)
SDI	93.21±0.17	71.22±0.05
SD2	93.39±0.03	76.11±0.55
SD3	95.63±0.07	87.55±0.76
SD4	97.81±0.11	94.77±0.44
SD5	91.50±0.06	70.16±0.63
SD6	92.23±0.01	74.69±0.58
SD7	95.68±0.44	84.39±0.64
SD8	96.72±0.76	93.29±0.13
SD9	97.12±0.16	95.13±0.72

Percentage drug release: In-vitro dissolving experiments demonstrated that all formulations had an influence on the amount of medication that was actually released. It was discovered that the percentage of solid dispersions that were released after one hour ranged from 80.10 percent to 95.63 percent. In Table 4, the cumulative percentage of medication that was delivered at different time intervals for each formulation is shown in the following manner.

Table 4: Percentage drug release of Solid dispersions

Time (min)	Percentage drug release								
	SDI	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD9
0	0	0	0	0	0	0	0	0	0
10	25.07±0.26	27.48±0.12	29.99±0.35	33.55±0.41	24.80±0.37	25.25±0.64	28.72±0.75	32.54±0.38	31.54±0.38
30	64.38±0.18	68.94±0.22	71.47±0.47	74.36±0.12	64.05±0.21	65.1 1±0.69	68.50±0.45	70.61±0.53	69.61±0.53
45	70.81±0.34	73.48±0.48	77.81±0.14	80.37±0.53	69.08±0.72	70.35±0.25	73.96±0.58	78.28±0.25	79.28±0.25
60	81.24±0.62	83.94±0.38	87.85±0.64	95.63±0.16	80.10±0.25	82.65±0.38	85. 14±0.22	94. 17±0.43	96.17±0.43

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Selection of Polymer: Choosing the Right Polymer In order to choose the most suitable polymer for the production of solid dispersions, SD1, SD2, SD3, and SD4 were created with PEG 6000, while SD5, SD6, SD7, and SD8 were prepared with HPMC K100M. According to the findings of the SD studies described above, it was discovered that the solid dispersions that were made using PEG 6000 produced superior outcomes when compared to other formulations. Additional statistical optimization of the formulation was performed with the help of the statistical software trial package Design Expert 10 and Stat – Ease 10.0.3.1.

OPTIMIZATION OF SOLID DISPERION

Preparation of different formulations of Solid dispersions:

There were a number of various ratios of solid dispersions that were generated, and factors such as the quantity of PEG 6000 and the amount of methanol were used to determine the optimal formulation.

Table 5: Formulation Table of optimized Solid dispersions Runs Formulation Code Amount of Carvedilol (gm.)

Runs	Formulation Code	Amount of Carvedilol (!!m.)	Amount of PEG 6000 (!!m.)	Amount of methanol (ml)
I	F1SD	I	2	3
2	F2 SD	I	2	4
3	F3 SD	I	2	*5*
4	F4 SD	I	3	4
5	F5 SD	I	3	3
6	F6 SD	I	3	5
7	F7 SD	I	4	*5*
8	F8 SD	I	4	4
9	F9 SD	I	4	3

Characterization of optimized

SD Dissolution rate of Solid dispersions

Table 6: Percentage drug release of Solid dispersions

	Percentage drug release								
	SDI	**SD2**	**SD3**	**SD4**	**SD5**	**SD6**	**SD7**	**SD8**	**SD9**
0	0	0	0	0	0	0	0	0	0
10	26.17±0.15	28.24±0.34	27.20±0.22	31.34±0.18	29.27±0.46	30.31±0.32	32.38±0.42	33.41±0.27	33.41±0.33
15	48.32±0.54	50.06±0.13	46.88±0.38	53. 17±0.29	51. 10±0.31	52.13±0.28	54.42±0.44	56.29±0.15	55.24±0.51
30	68.76±0.14	69.76±0.32	67.67±0.58	71.88±0.39	70.84±0.22	71.88±0.27	72.93±0.38	75.00±0.17	73.96±0.25
45	74.04±0.63	75.04±0.35	72.95±0.29	78. 17±0.73	76.10±0.58	77. 14±0.46	79.92±0.24	81.30±0.56	80.26±0.14
60	83.33±0.75	84.41±0.68	83.36±0.49	88.63±0.52	86.50±0.23	87.59±0.48	93.82±0.55	95.89±0.39	94.85±0.23

Drug content: In table 7, the proportion of drug content that was present in the formulations of the solid dispersions was shown. It can be seen that the formulations with a low polymer ratio resulted in a relatively low amount of medication content. A high drug content was obtained from the formulation that had a greater polymer ratio.

Table 7: Percentage drug content of Solid dispersions

Formulation	**Drug Content** (%)
F1SD	72.78±0.12
F2 SD	78.10±0.27
F3 SD	77.10±0.22
F4 SD	88.88±0.43
F5 SD	84.00±0.36

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F6 SD	87.01±0.25
F7 SD	93.20±0.3 1
F8 SD	95.21±0.14
F9 SD	94.06±0.46

Solubility Analysis: Table no. 8 provides information on the solubility of the formulations of the solid dispersions as well as the solubility of pure Carvedilol in water. In accordance with the data shown in the table, the solubility of the formulations improves as the concentration of the polymer that is used rises.

Table 8: Solubility study of Solid dispersions

Formulation	Solubility (mg/ml)	Solubility enhancement ratio
Pure drug	0.0093	-
F1SD	0.0597	06
F2 SD	0.0798	08
F3 SD	0.0697	07
F4 SD	0.1013	11
F5 SD	0.0855	09
F6 SD	0.0913	10
F7 SD	0.1100	12
F8 SD	0.1350	15
F9 SD	0.1287	14

DEVELOPMENT OF THE OPTIMUM SD BATCH

The program provided a solution for achieving the greatest percentage of drug release, drug content, and solubility enhancement ratio of the SD formulations. This solution was based on the statistical assessments. Additionally, the percentage of drug release, the amount of drug present, and the solubility enhancement ratio were provided along with the formula that was selected for the subsequent investigations.

Table 9: Formula for optimum SD batch based on statistical evaluations.

Number	Amount of PEG 6000 (gm.)	Amount of methanol (ml)	Dissolution at 60^{th} min (%)	Drug content (%)	Solubility enhancement ratio
I	4	3.825	95.788	95.9 15	14.858

EVALUATION OF OPTIMIZED SD

The SD formulations were examined using a variety of analytical techniques, including FTIR, SEM, Powder X-ray diffraction, and DSC. The percentage yield, drug content, and dissolution at 60 minutes were also analyzed. Table serves as a representation of the assessment.

Table 10: Evaluation of optimized SD formulation

Time (min)	Percentage(%) drug release of Optimized SD
0	0
10	33.41
15	54.21
30	73.96
45	81.30
60	95.89

Scanning Electron Microscopy Analysis: Based on the results of the scanning electron microscopy analysis, the following is the shape and surface morphology of the pure medication and the SD formulations. It is a qualitative

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approach that is used to examine the structural characteristics of SD and pharmaceuticals, or the products that are created using various ways of production. SEM is a method that is employed. It is anticipated that scanning electron microscopy (SEM) imaging of solid dispersion would offer information on the surface morphology. It is possible to use the morphological changes that have occurred in these structures as evidence that a solid dispersion has been formed. The research demonstrates that the crystal structure of the medication has shifted to an amorphous form. The increase in solubility may be attributed to this modification in the crystal pattern. In terms of their microscopic structure, the drug and the solid dispersion of the drug were found to be significantly different.

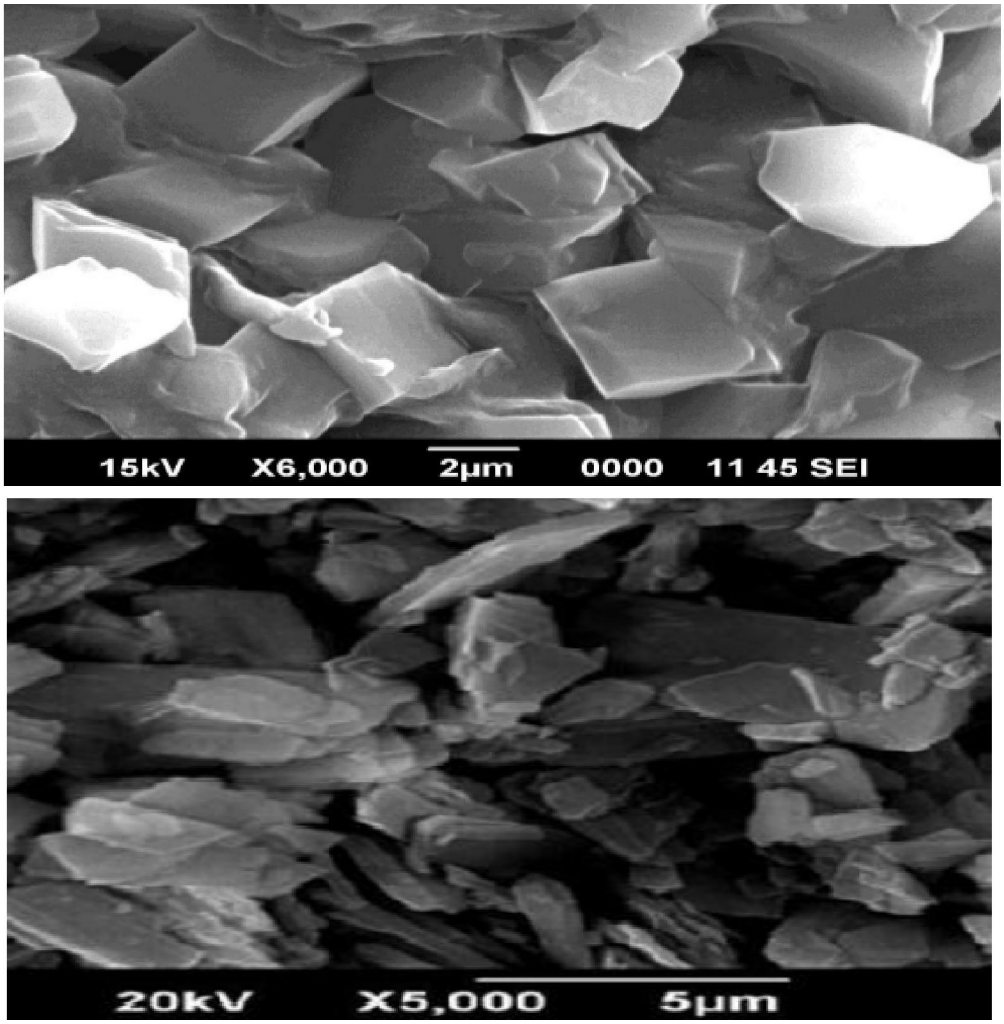

Figure 4: SEM picture of Pure drug (Carvedilol)

Differential scanning calorimetry study (DSC): For the purpose of examining the thermal behavior, both the pure medication and the formulation of the solid dispersion were subjected to DSC analysis. The DSC thermograms of the medication and the solid dispersion are shown in figures 8 and 9, respectively. A further piece of evidence indicating solid dispersions were created was supplied by the DSC study. As a result of the formation of solid dispersions, the melting, boiling, and sublimation points of the dispersions changed to other temperatures or vanished entirely. At a temperature of 1200 degrees Celsius, the DSC thermogram of the pure medication Carvedilol reveals an endothermic peak. This peak is associated with the melting point of the pure drug. This demonstrates that the carvedilol that was used was in its purest form, a crystalline condition. The absence of a prominent endothermic peak in the DSC thermogram of the carvedilol solid dispersion, which is distinct from the sample of pure drug, is indicative of the creation of the solid dispersion.

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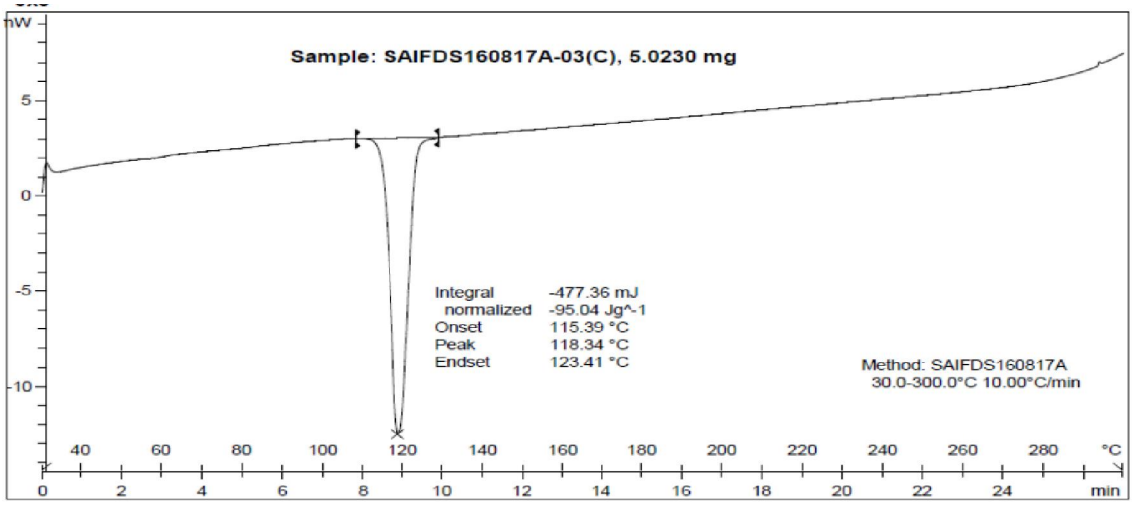

Figure 5: DSC thermogram of Carvedilol

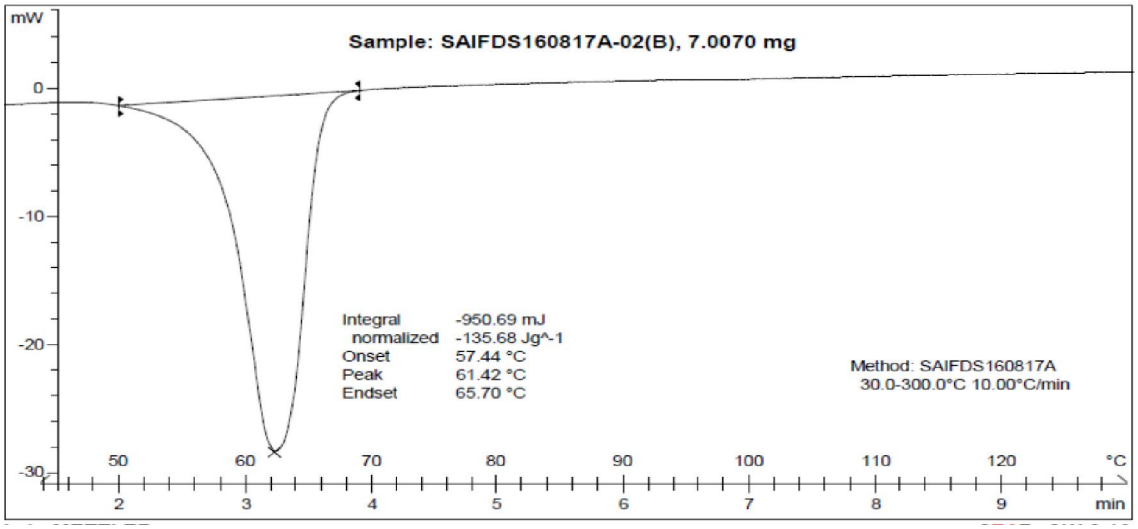

Figure 6: DSC thermogram of Solid dispersions

IV. CONCLUSION

In conclusion, the formulation and evaluation of solid dispersions have proven to be an effective strategy in enhancing the solubility, dissolution rate, and consequently, the bioavailability of carvedilol. The comprehensive characterization studies, including FTIR, DSC, PXRD, and SEM, elucidated the interactions between the drug and carriers, solid-state modifications, and morphological features, providing valuable insights into the formulation development. The in vitro dissolution studies demonstrated significant improvements in drug release profiles compared to the pure drug formulation. Moreover, pharmacokinetic evaluations in animal models exhibited enhanced bioavailability of carvedilol from the optimized solid dispersion formulation. Future research endeavors could focus on further optimizing the formulation parameters, exploring novel carriers, and investigating innovative techniques such as nanosizing or complexation to enhance the efficiency of carvedilol solid dispersions. Additionally, long-term stability studies under various storage conditions would be beneficial to ensure the robustness and reproducibility of the optimized formulation. Furthermore, exploring the correlation between in vitro dissolution profiles and in vivo performance through advanced modeling and simulation techniques could offer deeper insights into the formulation's predictive behavior in clinical settings, facilitating its translation into scalable and commercially viable pharmaceutical product

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